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PETER BERNSTEIN
SCULLY, SCOTT, MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 06/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,288	PEVARELLO ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-14,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-14, 21 and 22 are currently pending in the instant application and are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 18 April 2006 has been entered.

Response to Arguments

Applicant's arguments filed 18 April 2006 have been fully considered but they are not persuasive. Applicant argues that the specification explicitly teaches that the preferred compounds of formula (I) are those where R is a C3-C6cycloalkyl or an optionally substituted straight or branched C1-C4alkyl group, a cycloalkyl or an aryl or arylalkyl group and the more preferred compounds are those where R is a C3-C6 cycloalkyl, referring to page 11 and originally filed claim 8, and therefore the amendment to claims 1 and 15 and the specification is fully supported by the original disclosure. This argument is not persuasive, for essentially the same reasons as found in the final rejection mailed 14 June 2005. Specifically, the examiner has not argues that R cannot every be a C3-6 cycloalkyl, just that there is not support for R as C3-

6cycloalkyl in the generic compound claimed, i.e. R can be C3-C6 cycloalkyl when n is 0 and R1 is hydrogen, as found in the originally filed disclosure and original claim 1 from which claim 8 depends, but there is no support found in the originally filed disclosure for R to be C3-6 cycloalkyl when n is not 0 and R2 is not hydrogen, as instantly claimed. The specific species found in the specification only provide support for themselves, and the preferences, for example on page 11 of the specification, only support R as C3-C6cycloalkyl when n is 0 and R2 is hydrogen. One of ordinary skill in the art would not recognize the existence of an error or the appropriate correction. Therefore, as previously argued in the final office action of June 2005, the originally filed disclosure does not provide support for R as C3-6cycloalkyl when n is 1-5 and/or R1 and R2 together with the nitrogen atom form a heterocycle or heteroaryl. In regards to the 35 USC 112 1st paragraph enablement rejection, applicant argues that the specification contains sufficient information regarding the subject matter of the claims as to enable one skilled in the art to make and use the claimed methods of treating cell proliferative disorders without undue experimentation as the specification need not disclose what is well-known to those skilled in the art. Applicant also argues that the claimed method of administering a compound of formula (I) to a mammal in need thereof for the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity is commensurate in scope with the disclosure of the present application and does not specify whether "HIV and Alzheimer's disease" is included in the claimed disorder. . Applicant argues that direct inhibition of cdk/cyclin kinase activity can restrict the unregulated tumor cell proliferation and that the present invention provides detailed

experimental protocol that the compounds of formula (I) are active as cdk/cyclin inhibitors and pharmacological protocols such as dosage are provided. This argument is not found persuasive as applicants' originally filed claim 2 provides a limitation of cell proliferative disorders associated with an altered cell dependent kinase activity to include cancers, Alzheimer's disease and virus infections (which would include HIV). Furthermore, the treatment of cancer is not a reasonable correlation to the entire scope of claim 1 as treating any cell proliferative disorder. The broad treatment of cancer does not find enablement in the instant specification as it is known in the prior art that the cancer therapy remains highly unpredictable, that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy, that treatment against tumors with rapidly dividing cells can differ from the treatment of solid tumors with relatively slow dividing cells and that both the promotion and inhibition of NO is mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. Since the cancer therapy is highly unpredictable, one of ordinary skill in the art would not accept any therapeutic regiment on its face and there is a more specific enablement necessary in order to satisfy the statute. Furthermore, there is no support found in the instant application for the treatment of cancer, i.e. there is no direction or guidance or working examples to show the treatment of any and all cancers with applicants' instant formula (I).

Maintained Specification Objection

The amendment filed 3 November 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment to pages 3 and 4 wherein R is a C3-C6 cycloalkyl group, which is optionally substituted with a straight or branched C1-C6alkyl group and the amendment to pages 5 and 6 wherein R is a C3-C6 cycloalkyl group, which is optionally substituted with a straight or branched C1-C6alkyl group. Applicant points to support for this amendment on pages 4, lines 29-30, page 6, lines 24-25 and in the last clause of each of original claims 1 and 15 and further on page 11, lines 9-10. However, the statement that applicant relies upon for support of the amendment, "provided that when n is 0 and R2 is hydrogen, R is a C3-C6 cycloalkyl group optionally substituted with a straight or branched C1-C6 alkyl group" does not provide support for this amendment. The statement that applicant refers to for support on the various pages and claims only provides support for R being a C3-C6 cycloalkyl group when n is 0 and R2 is hydrogen. Support is not provided for R being a C3-C6 cylcoalkyl group when n is 1-4 and/or R2 and R1, together with the nitrogen atom to which they are bonded, form a heterocyclyl or heteroaryl group. While there are numerous specific species of compounds found in the specification and claims which contain R as a C3-C6 cyclalkyl group when n is not 0 and/or R2 is not hydrogen, this also does not provide support for the amendments mentioned above since these specific compounds only provide support for themselves and not an amendment to a

broad genus claim which encompasses other combinations and compounds wherein R as a C3-C6 cycloalkyl group when n is not 0 and R2 is not hydrogen which do not find support in the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-12, 14, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the amendment to claims 1 and 15, filed 4 November 2003, to include wherein R is a C3-6 cycloalkyl group, which is optionally substituted with a straight or branched C1-C6 alky group, does not find support in the original disclosure and is considered new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant points to support for this amendment on pages 4, lines 29-30, page 6, lines 24-25 and in the last clause of each of original claims 1 and 15 and further on page 11, lines 9-10. However, the statement that applicant relies upon for support of the amendment, "provided that when n is 0 and

R2 is hydrogen, R is a C3-C6 cycloalkyl group optionally substituted with a straight or branched C1-C6 alkyl group" does not provide support for this amendment. The statement that applicant refers to for support on the various pages and claims only provides support for R being a C3-C6 cycloalkyl group when n is 0 and R2 is hydrogen. Support is not provided for R being a C3-C6 cylcoalkyl group when n is 1-4 and/or R2 and R1, together with the nitrogen atom to which they are bonded, form a heterocyclyl or heteroaryl group. While there are numerous specific species of compounds found in the specification and claims which contain R as a C3-C6 cyclalkyl group when n is not 0 and/or R2 is not hydrogen, this also does not provide support for the amendments mentioned above since these specific compounds only provide support for themselves and not an amendment to a broad genus claim which encompasses other combinations and compounds wherein R as a C3-C6 cycloalkyl group when n is not 0 and R2 is not hydrogen which do not find support in the original disclosure. Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 1-3 and 5-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a

disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claims 1-14 is the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity with the compound of the formula (I). Pages 4 and 5 discloses that in the preferred embodiment the cell proliferative disorder is selected from cancer, Alzheimer's disease, viral infections (which includes HIV), autoimmune diseases and neurodegenerative disorders.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in

the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the above listed diseases, whether or not the disease is effected by the inhibition of cdk/cyclin kinase would make a difference.

Applicants are claiming a method of treating the diseases listed in the claims such as viral infections, which includes HIV, by administering a compound of the formula (I). As such, the specification fails to enable the skilled artisan to use the compounds of the formula (I) to treat HIV. In addition, there is no proof that the claimed compounds have ever been administered to a human or to an animal model. The obstacles to therapeutic approaches and vaccine development with regard to retroviruses associated with AIDS in humans are well documented in the literature. See, for example, Huff {J. Med. Chem. 34(8) 1991, p. 2305-2314} on page 2314. These obstacles include and are not limited to : 1) the extensive genomic diversity associated with HIV, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which

pass the infecting virus to other cells in a convert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to traverse the blood brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting therapeutic regimen on its face. In addition, there is no established correlation between in vitro activity and accomplishing treatment of viral infections, especially HIV infections, in vivo, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use the compounds of the formula (I) since there is no description of an actual method wherein a viral infection in a host is treated.

Applicants claims also include the treatment of any cancer. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala

et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Applicants claims are also drawn to the treatment of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the inhibition of cdk/cyclin kinase, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the inhibition of cdk/cyclin kinase, and since HIV, a viral disease is known to have many obstacles that would prevent one of ordinary skill in the art from accepting therapeutic regimen on its face, since various types of cancers have different causative agents, involve different cellular mechanisms and differ in treatment protocol and since it is known that there is no known cure for

Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as cell proliferative disorders associated with an altered cell dependent kinase activity, pages 2, 3 and 5. Cdk/cyclin kinase assays are found on pages 24-26. There are no working examples present for the treatment of any cell proliferative disorder.

The breadth of the claims

The breadth of the claims is the treatment of any cell proliferative disorder associated with an altered cell dependent kinase activity with any compound of the formula (I). Cell proliferative disorders, include, for example, as found on pages 4 and 5 of the instant specification, cancer, Alzheimer's disease, viral infections (which includes HIV), autoimmune diseases and neurodegenerative disorders.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated) by the inhibition of cdk/cyclin kinase and would furthermore then have to determine which of the claimed compounds would provide treatment of which disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment of any cell proliferative disorders associated with an altered cell dependent kinase activity. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
5/13/06

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600